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14. ABSTRACT
Oxidative stress, which results from an imbalance between ROS and antioxidant capacities, can cause a wide range of direct or indirect DNA damage. There are extensive DNA repair systems that can correct DNA damage caused by ROS before cell replication and mutation fixation. Although oxidative stress appears to be important in the etiology of prostate cancer, so far there is no study to comprehensively investigate the association between DRC of oxidative DNA damage as a phenotype and prostate cancer risk. We hypothesize that DRC of oxidative DNA damage as a phenotype may modify prostate cancer risk. So far, the study has recruited 156 cases and 132 controls. The proposed molecular analysis has begun for all three specific aims.

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Introduction

Many of the known and suspected risk factors for prostate cancer are associated with elevated levels of ROS (advancing age, inflammation, androgen, high-fat diet), or decreased antioxidant capabilities (fruit and vegetable consumption, specific dietary antioxidants, such as selenium, vitamin E and carotenoids). Oxidative stress, which results from an imbalance between ROS and antioxidant capacities, can cause a wide range of direct or indirect DNA damage. There are extensive DNA repair systems that can correct DNA damage caused by ROS before cell replication and mutation fixation. For instance, ROS-caused base damages and single strand breaks are mainly repaired by BER and NER; DNA adducts caused by ROS-induced lipid peroxidation are repaired by NER; and ROS caused-DNA double strand breaks are repaired by HRR and NHEJ. However, DRC is substantially variable among individuals in the population, and suboptimal DRC of oxidative DNA damage might increase genomic instability and hence, increase risk of cancer. Although oxidative stress appears to be important in the etiology of prostate cancer, so far there is no study to comprehensively investigate the association between DRC of oxidative DNA damage as a phenotype and prostate cancer risk.

Body

Study subject recruitment: At the end of September of 2009, we have recruited 156 men diagnosed with prostate cancer as cases and 132 healthy men as controls. Both cases and controls were recruited through DataBank BioRepository (BDDR) of Roswell Park Cancer Institute (RPCI). On average, we have around 15 cases and 15 controls per month. We don't expect any significant delay to recruit 300 cases and 300 controls.

Specific aim 1: we will measure levels of 8-OH-dG after exposure to H_2O_2 in PBLs in 300 men with prostate cancer and 300 healthy controls, using ELISA based mutagen sensitivity assay. Our hypothesis is that cases will exhibit higher levels of 8-OH-dG after exposure to H_2O_2 (reflecting lower BER activity) compared with healthy controls. So far, the proposed 8-OH-dG analysis has been carried out in 98 prostate cancer cases and 87 healthy controls. The mean levels of 8-OH-dG were significantly higher in cases than in controls (4.52 vs. 3.11, $P<0.01$). In further stratified analysis, using median levels of 8-OH-dG in controls as the cutoff point, we found higher levels of 8-OH-dG was associated with 1.45-fold increased prostate cancer risk (OR= 1.45, 95% CI: 1.04 to 2.35).

Specific aim 2: we will assess levels of DRC of DNA adducts induced by 4-HNE in PBLs in 300 prostate cancer cases and 300 healthy controls, using plasmid based modified HCR assay. 4-HNE is a major product of endogenous lipid peroxidation. 4-HNE caused DNA adducts is mainly repaired by NER. Our hypothesis is that cases will exhibit lower levels of NER of 4-HNE caused DNA adducts compared with healthy controls. So far, the proposed 4-HNE based host cell reactivation (HCR) assay has been carried out in 75 prostate cancer cases and 77 healthy controls. The mean levels of 4-HNE based HCR were marginally lower in cases than in controls (6.7% vs. 8.6%, P=0.052). In further stratified analysis, using median levels of 4-HNE based in controls as the cutoff point, we found lower levels of 4-HNE based was not associated with the prostate cancer risk (OR= 1.21, 95% CI: 0.75 to 1.89). Because of the small sample size, we have to be very cautious to interpret the results.

Specific aim 3: we will assess levels of HHR and NHEJ of double strand breaks in PBLs in 300 men with prostate cancer and 300 healthy controls, using plasmid based modified HCR assays. Our hypothesis is that cases will exhibit lower levels of HR and NHEJ compared with healthy controls. For HR assay, the assay has been carried out in 54 prostate cancer cases and 47 healthy controls. The mean levels of HR activity were lower in cases than in controls (10.5% vs. 12.4%, P=0.34), but the difference didn't reach statistically significant. For NHEJ assay, the assay has been carried out in 54 prostate cancer cases and 47 healthy controls. The mean levels of HR activity were lower in cases than in controls (7.9% vs. 8.9, P=0.44), but the difference didn't reach statistically significant.

Overall, we expect to complete the proposed analyses on time. No major delay is forecasted.

Key Research Accomplishments

1. At the end of September of 2009, we have recruited 156 men diagnosed with prostate cancer as cases and 132 healthy men as controls. We don't expect any delay in the study subject recruitment.

2. The proposed molecular analyses in specific aims 1-3 have run well. We expect to complete the proposed analyses on time.

3. We have obtained questionnaire data from 156 patients and 132 controls.

4. In training, Dr. Mohler (the mentor) has regularly consulted the project. Dr. Zhao has also involved in Dr. Mohler's other research project.

Reportable outcomes

Because the study is still ongoing, at this point, we don't have any manuscript in preparation. But, we expect to begin to prepare two manuscripts pretty soon.

Conclusion

The study has run smoothly so far. We don't expect any delay.